

Nonuniform Deposition of Pressurized Metered-Dose Aerosol in Spacer Devices

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Abstract

Background: Pressurized metered-dose inhalers (pMDIs) are commonly used to administer medication to patients suffering from chronic lower respiratory tract diseases such as asthma. Inhaling medication directly from a pMDI can prove difficult for some patients and, as a result, add-on devices (or spacers) have been designed to aid in the delivery of medication. Although spacers increase the percentage of medication that reaches the patient, medication will also nonsymmetrically deposit on the walls of the device and will be lost to the device itself.

Methods: The deposition of medication, salbutamol sulfate, within a large- and a small-volume spacer, has been studied through an experimental and numerical analysis. Experiments were conducted at inspiratory flow rates ranging from 30 to 60 L/min. The amount of deposition of the medication on the walls of the spacer was quantified through an application of spectrophotometry. Computational fluid dynamics was used to quantify the deposition numerically. Simulations were conducted by implementing mean flow and turbulent tracking of particles using unsteady Reynolds-averaged Navier–Stokes (URANS) equations with a shear stress transport turbulence model. Regions of deposition are of interest, as well as how the method of deposition varied for different inhalation flow rates.

Results and Conclusions: The deposition of salbutamol sulfate in the Volumatic® and OptiChamber® spacers was found to be greater in the lower half as opposed to the upper half of the spacer due to a downward spray angle. With an increased flow rate, these spacers demonstrated a slight increase in medication delivered to the inline filter, which is analogous to that reaching the patient, and an increase in distal deposition. For the numerical analysis, the results indicated that inertial impaction is the most likely method of deposition for the Volumatic spacer, and turbulence is more likely to cause deposition in the OptiChamber spacer.

Key words: asthma, computational fluid dynamics, pressurized metered-dose inhaler, shear stress transport, spacer, spectrophotometry, unsteady Reynolds-averaged Navier–Stokes

Introduction

LOWER RESPIRATORY TRACT diseases directly affect the respiratory system by causing difficulties in breathing due to airway inflammation. Asthma is one such disease that presents with shortness of breath, chest tightness, and coughing.⁽¹⁾ During an asthma attack, the bronchi and bronchioles will constrict, resulting in increased resistance to airflow and is accompanied by elevated mucus production and inflammation of the bronchi. Reliever medications, such as β_2 -agonists, are commonly used to provide short-term relief of asthma symptoms once the airways become inflamed. β_2 -agonists target $ADR\beta_2$ in the bron-

chial muscles and cause bronchodilation within 10–15 minutes. Salbutamol sulfate is a regularly prescribed β_2 -agonist reliever medication.⁽²⁾

Pressurized metered-dose inhalers (pMDIs) or “puffers” are widely prescribed aerosol delivery systems to treat lung diseases such as asthma. The pMDI design consists of three parts: an actuator, a metering valve, and a pressurized canister.⁽³⁾ Upon actuation, the pMDI releases a spray, which is transient, turbulent, three-dimensional, and multiphase, creating a complex numerical analysis.⁽⁴⁾

Aerosol medication released directly from a pMDI tends to deposit in the oropharyngeal tract and oropharynx region before reaching the treatment area, the small airways. As a

result, as little as 10% of the medication released from a single dose of the pMDI will actually reach the lungs.⁽⁵⁾

Add-on devices such as spacers have been developed to enhance the total amount of aerosol medication delivered to the lungs. Spacers available on the market commonly have a diamond or cylindrical shape and some contain valves that open under specific inspiratory flow rates. Thorsson et al.⁽⁶⁾ present that a spacer attached to a pMDI can increase delivery of medication to the lungs by ~20% as opposed to using a pMDI alone.

A spacer device primarily acts to aid in the inhalation of medication despite asynchrony of the actuation of the pMDI and the inhalation of the medication by the patient. In addition, a spacer also tends to reduce the “cold Freon effect,” which is a result of the propellant cooling the medication during evaporation. When the cold plume of medication impacts the oropharynx of a patient, inspiration is hindered by a muscle reflex.⁽⁷⁾ Due to the length of the spacer, there is an increased distance between the throat and the actuator, and the propellant has enough time to evaporate and to increase the temperature of the gas. This reduces and nearly eliminates the cold Freon effect. The length of the spacer also provides enough time for the medication to lower its velocity resulting in less inertial impaction of medication in the oropharyngeal tract and oropharynx.

Geometrical parameters of a spacer can also effect the amount of drug respirable from the spacer itself. Barry and O’Callaghan⁽⁸⁾ found that an increase in spacer diameter and length increased the amount of drug recovered. Previous work conducted using Particle Image Velocimetry (PIV) measurements of spray velocity indicate that the spray angle from a pMDI varies with time, moving downward to -6° and deflecting back to 0° to the spray axis during actuation.⁽⁴⁾

The current study focused on the measurement and simulation of pMDI nonsymmetrical aerosol deposition on the walls of a spacer device. The regional deposition of salbutamol sulfate within a spacer was studied for different inhalation flow rates through spectrophotometry and computational fluid dynamics (CFD). By better understanding the physics involved in this aerosol deposition, more efficient spacer designs or a redesign of the pMDI actuator itself may be developed.

Material and Methods

Experimental procedure

Experiments were performed to determine the behavior of salbutamol sulfate aerosol particles within a large- and small-volume spacer device. The large-volume spacer used was the 750 mL volume Volumatic[®] spacer (Allen and Hanburys Ltd., London, England) as displayed in Figure 1. In addition, a 218 mL volume OptiChamber[®] spacer (HealthScan Products, Inc., Cedar Grove, NJ) was tested (as displayed in Fig. 2).

Both spacers were used with a Novo-Salbutamol HFA (TEVA Pharmaceutical Industries Ltd., Toronto, Canada) pMDI containing salbutamol sulfate. The main objectives of the experiment were to quantify the amount of salbutamol sulfate that remained within the spacer after actuation, the regions within the spacer where deposition is most concentrated, and the main cause of deposition.

The method used by Alhegagi and Matida⁽⁹⁾ and Alhegagi⁽¹⁰⁾ was utilized, through which a vacuum pump was used to simulate three different inspiratory flow rates of 30, 45, and 60 L/min. These flow rates ranged from just above the breathing rate during moderate exercise to the recommended flow rate for use of a pMDI without a spacer. The equipment used was an Agilent 8453 UV-Visible Spectrophotometer (Agilent Technologies, Santa Clara, CA), a Brooks Mass Flow Meter[®] 5863S (Brooks Instrument, LLC., Hatfield, PA), a National Instruments[™] Data Acquisition USB-6009 device (National Instruments Corporation, Austin, TX), and a Welch[®] Dry Vacuum Pump 2585B (Welch-Illvac, Niles, IL). The Agilent Spectrophotometry system and the data acquisition device were connected to a computer to take instrument readings with Agilent and LabVIEW[™] software, respectively. Figure 3 shows an experimental schematic of the apparatus.

To study regional deposition, each spacer had to be divided into quarters (upper and lower front sections, upper and lower back sections) as seen in Figures 4 and 5. To do this, models of both the Volumatic and OptiChamber spacers were produced using CREO[®] SolidWorks software and the Dimension BST 3D ABS printer (Stratasys, Eden Prairie, MN). The quadrants were attached together using dowel pins at fixed positions and medical tape. The geometry was wrapped with Parafilm[™] to ensure no medication was released to the surroundings. For the large-volume spacer, an adapter was also modeled to fit the distal sections of the spacer to a Respigard II[™] filter (Vital Signs, Inc., Totowa, NJ). This filter would capture any medication leaving the spacer, which is analogous to the amount of medication depositing in the lungs and the oropharynx.

Using one foot of 12.7-mm-diameter rubber tubing, the filter was attached to a flow meter. The flow meter was then connected in sequence to a flow control valve by another foot of tubing. The flow meter measured the flow rate, which was regulated by the flow control valve. Attached to the other end of the valve was a vacuum pump, which drew air

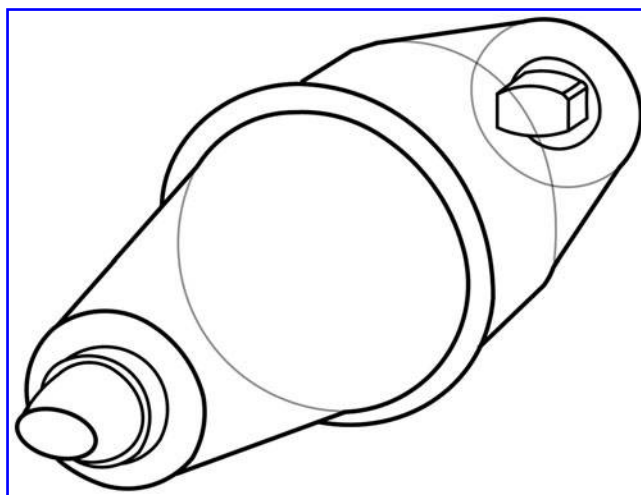


FIG. 1. Schematic of the Allen and Hanburys Volumatic spacer.

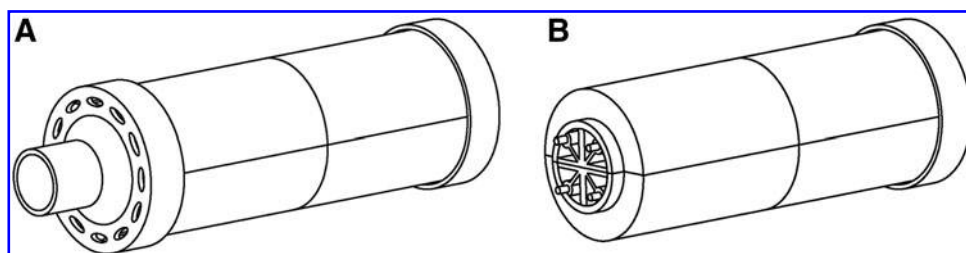


FIG. 2. Schematic of HealthScan Products OptiChamber spacer. (A) OptiChamber with mouthpiece attached. (B) OptiChamber with mouthpiece removed, exposing the valved portion of the spacer.

through the system to draw the aerosol droplets from the pMDI into the spacer and through the filter.

Before commencing the experiments, the spacer replicas were washed with dish soap and allowed to air dry. This minimized losses due to suspended particles from static charge on the spacer walls as discussed by Newman.⁽¹¹⁾ The spacer quadrants were assembled and the equipment was set up as displayed in Figure 3. Experiments were carried out at the specified flow rates using the flow control valve and the flow meter.

Once steady flow was reached, as reported by the flow meter, the pMDI was fired 20 times into the spacer and was vertically shaken once between each actuation to ensure a consistent dosage was delivered. After running the experiment, the actuator, the filter, and the quadrants of the spacer were separated to determine the deposition of salbutamol sulfate on each region. Each part was then washed using 20 mL of 20% ethanol solution. A 10-mL pipette was used to rinse each part before using a sterile cotton-tipped applicator to clean the surface. To clean the filter, 20 mL of 20% ethanol solution was passed through the filter using a pipette suction method as in Alhegagi⁽¹⁰⁾ and Alhegagi and Matida,⁽⁹⁾ which entailed coating one side of the filter with a thin layer of ethanol and drawing the ethanol solvent through the opposite end using a pipette.

The deposition of salbutamol sulfate for each flow rate could then be determined by measuring the absorbency of each wash solution. It was first necessary to generate a calibration curve, which would relate the measured absorbency to the concentration of salbutamol sulfate. To achieve this, a stock solution of salbutamol sulfate and 20% ethanol was prepared from 50 mg of pure salbutamol sulfate (Sigma

Aldrich Canada, Oakville, Canada). Using the stock solution, the salbutamol sulfate was diluted to known concentrations. These samples were run through the Agilent spectrophotometer and compared against a control sample of 20% ethanol solution. The absorbency of salbutamol sulfate was found at enough concentrations to generate a calibration curve.

Since salbutamol sulfate has a maximum absorption wavelength of 276–280 nm and a fixed wavelength node at an absorbency of 280 nm,^(9,10) a wavelength of 280 nm was used to quantify the absorbency of all samples. A blank of 20% ethanol solution was used as a control for all samples.

Three absorbency readings were taken for each sample of wash solution. From these absorbencies, the concentration of salbutamol sulfate could be found using the calibration curve relating absorbency to concentration. The deposition of salbutamol sulfate in the spacer could be found in micrograms since a known amount of solvent was used to dissolve the salbutamol sulfate (20 mL of 20% ethanol).

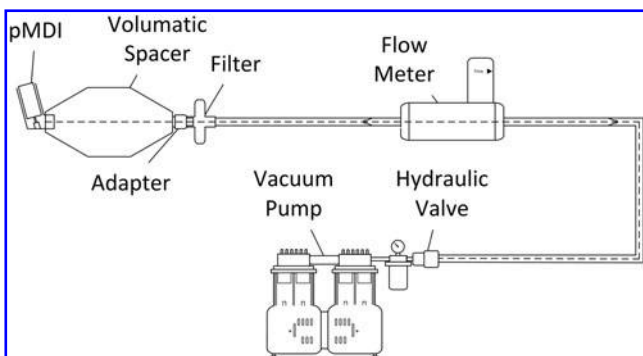


FIG. 3. Schematic drawings of experimental setup using a vacuum pump to draw pMDI aerosol through the spacer device. pMDI, pressurized metered-dose inhaler.

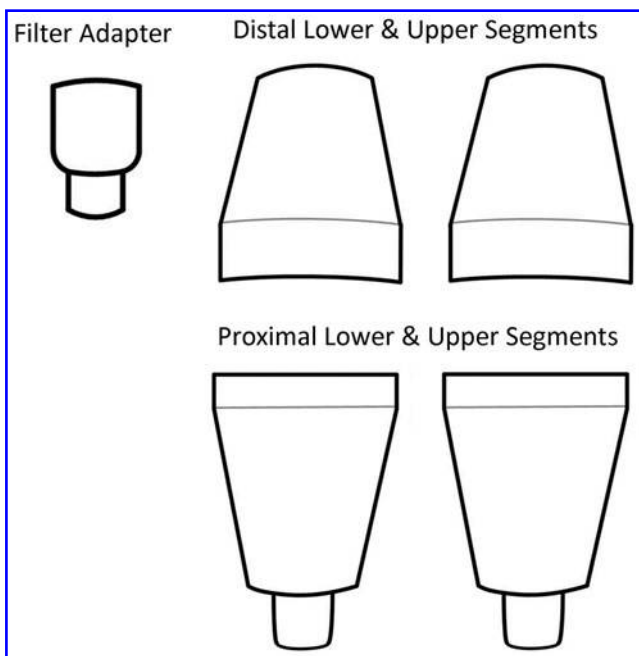


FIG. 4. Schematic of the components of the rapid prototyped Volumetric spacer. An adaptor was prototyped to attach the filter along with the four sections of the Volumetric spacer: distal lower, distal upper, proximal lower, and proximal upper.

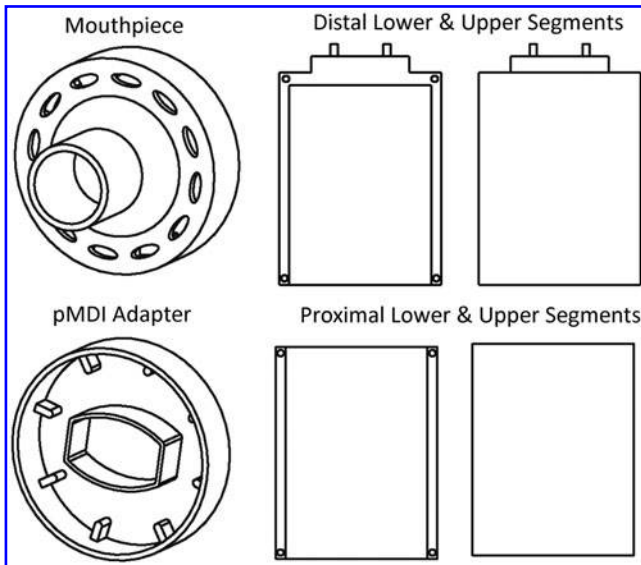


FIG. 5. Schematic of the components of the rapid prototyped OptiChamber spacer. A mouthpiece and an adaptor for the pMDI were prototyped along with the four sections of the OptiChamber: distal lower, distal upper, proximal lower, and proximal upper.

This experimental procedure was repeated thrice for each flow rate for reliability.

Numerical Analysis

Simulations were conducted using ANSYS CFX to numerically quantify the regional deposition of salbutamol sulfate in the Volumatic spacer. Due to its ability to conduct Lagrangian particle tracking and provide shear stress transport turbulence models, ANSYS CFX was a suitable choice of software.

Geometry

The geometry of the Volumatic spacer, OptiChamber spacer, and pMDI was generated in ICEM CFD as displayed in Figures 6 and 7.

The dimensions of the Volumatic spacer were reproduced with a total length of 230 mm and a maximum diameter of 90 mm. In addition, the OptiChamber was reproduced with a total length of 174 mm and a maximum diameter of 44 mm. The Volumatic spacer outlet was simplified by creating a straight rather than curved outlet to match that of the spacer replica. Four parts were created to study the regional deposition just as the spacer replica. An unstructured mesh for both spacers was created as shown in Figure 8. A grid of tetrahedral elements was generated using prism layers to capture detail near the boundary layers. The unstructured grid of the Volumatic spacer had $\sim 5,000,000$ tetrahedral elements, which was determined based on the results of a grid convergence analysis. Similarly, a grid convergence conducted for the OptiChamber spacer resulted in the use of an unstructured grid with $\sim 3,000,000$ tetrahedral elements. To study grid convergence, the velocity at the centerline and the horizontal and vertical components of the inlet to the spacer were selected and analyzed over different mesh sizes. When the variations of the velocity became independent of the mesh

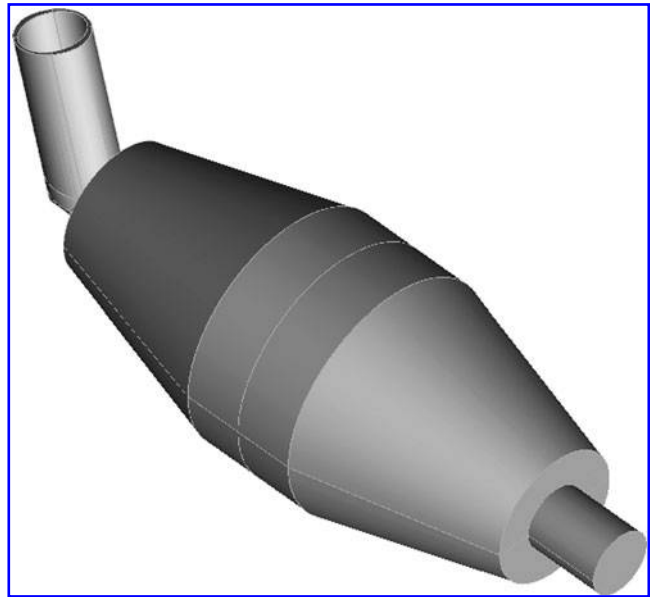


FIG. 6. Three-dimensional rendering of the Volumatic spacer and pMDI using ICEM by ANSYS.

size (i.e., changing the mesh size did not cause variations in velocity), the grid was considered to be converged. Steady-state simulations were performed at an inhalation rate of 60 L/min with a nozzle outlet velocity of 80 m/s at a constant downward angle of -6° to determine grid convergence.

Governing equations

Unsteady Reynolds-averaged Navier–Stokes (URANS) equations are used to study the behavior of the flow in the spacer. For transient flow, URANS equations ensemble average values. This reduces the computational power required to obtain a solution.

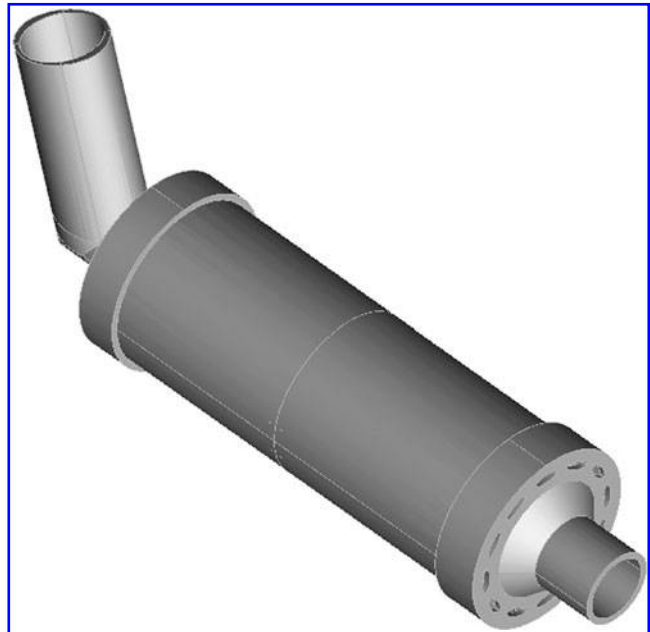


FIG. 7. Three-dimensional rendering of the OptiChamber spacer and pMDI using ICEM by ANSYS.

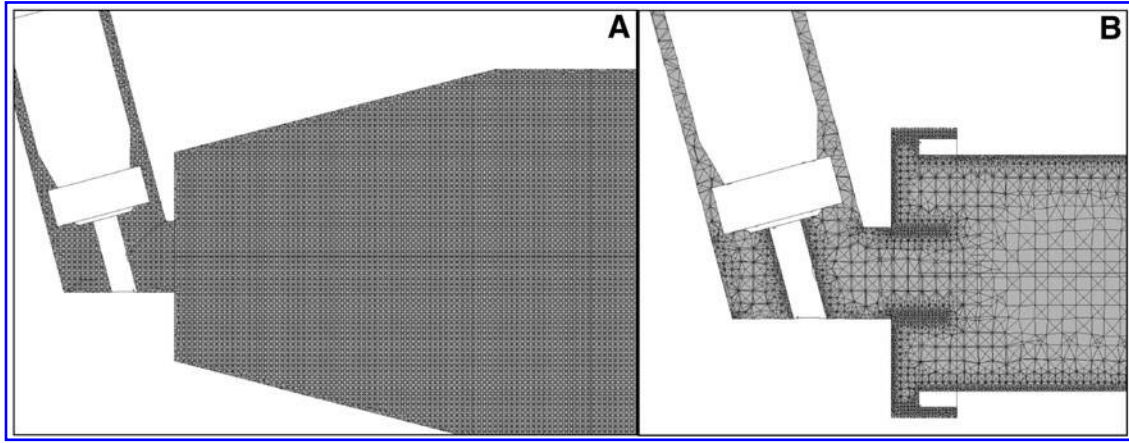


FIG. 8. Unstructured mesh of spacer geometry. (A) 5,000,000 Element unstructured mesh of the Volumatic spacer. (B) 3,000,000 Element unstructured mesh of the OptiChamber spacer.

A shear stress transport (SST) turbulence model is used to model the behavior of flow by incorporating both the $k-\omega$ and $k-\epsilon$ turbulence models. The SST model combines the accuracy of the $k-\omega$ model near the boundary layer and the detail of the $k-\epsilon$ model in the free-stream area outside the boundary layer.

The major problem of other models such as the Baseline (BSL) $k-\omega$ or the Wilcox $k-\omega$ is that they do not account for turbulent shear stress transport. As such, many models overpredict eddy viscosity. The SST model acts to reduce this overprediction through the use of a limiter on eddy viscosity. This limiter redefines the eddy viscosity as follows:

$$v_t = \frac{a_1 k}{\max(a_1 \omega, \Omega F_2)} \quad (1)$$

where F_2 is a blending function, restricting the limiter of eddy viscosity to the wall boundary layer, Ω is a measure of strain rate, k is the turbulence kinetic energy (m^2/s^2), ω is specific turbulence dissipation rate ($1/\text{s}$), and a_1 is a constant.

The use of a limiter and the blending function F_2 leads to accurate predictions of the onset and development of flow

separation since it allows for better estimates of the transport of turbulent shear stress. This makes the SST turbulence model suitable for wall bounded flow.⁽¹²⁾

Grid convergence

A grid convergence study was conducted to ensure that a suitable number of elements were used to generate the mesh, and small enough time steps were used to capture sufficient accuracy for the simulations. A large amount of elements and small time steps require more computational power, and so, grid convergence studies provide the optimal to ensure sufficient accuracy is provided with minimal computational power.

Convergence studies conducted for the Volumatic and OptiChamber spacers indicated that a mesh of 5,000,000 and 3,000,000 elements, respectively, would produce similar results to a mesh with a greater amount of elements but required less time to converge. Temporal analyses found that a suitable time step will achieve a Courant number, which will remain below one at each iteration. This is known as the CFL condition⁽¹³⁾ and can be calculated as follows:

$$C = \frac{u \times \Delta t}{\Delta x} \leq 1 \quad (2)$$

where C is the Courant number, u is the magnitude of the velocity (m/s), Δt is the time step (s), and Δx is the length interval (m).

Over the first 100 milliseconds of the simulation, a time step of 0.1 millisecond was selected to capture detail during the actuation of the pMDI. After the actuation, a time step of 1 millisecond was used to save on computation time. A total simulation time of 5 seconds was selected as to provide enough time to allow the particles to completely travel through the spacer or settle on the walls.

Nozzle inlet

A simplified inlet condition was produced to allow for the pMDI spray to deflect downward to -6° and back to 0° to the spray axis during the actuation as reported by Crosland et al.⁽⁴⁾ To do this, the inlet was placed downstream of the actual nozzle, adjacent to the actuator cylindrical stem. The diameter was increased to 1.49 mm from the actual nozzle

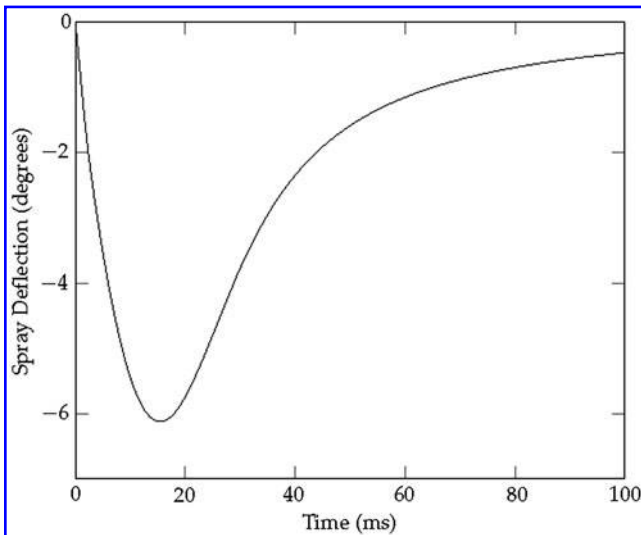


FIG. 9. Inlet spray angle as a function of time.

diameter of 0.25 mm to allow for more accurate meshing of the nozzle inlet. The nozzle inlet angle (in degrees) can be described by the following equation⁽¹⁴⁾:

$$\alpha = -\frac{1490.5}{t^{1.75}}[1 - \exp(-0.000727t^{2.5})] \quad (3)$$

The development of the spray angle can be seen in Figure 9.

Particle tracking

Multiphase flow was modeled to provide an accurate simulation of the behavior of salbutamol sulfate in the spacers. To initialize the simulations, 10,000 particles were released into the domain over 100 milliseconds (the actuation time of the puffer) from the nozzle inlet at 80 m/s. For simplicity, one-way coupling was used to describe the particulate phase. Simulations were performed using a Rosin–Rammner distribution with a spread parameter of 1.44 and a size constant of 12.2 μm , which corresponds to the distribution of the salbutamol particles used by Sprigge.⁽¹⁵⁾ Salbutamol sulfate was specified as a particle transport fluid with a Schiller–Naumann drag model, used to model the drag around the particles. The Schiller–Naumann drag model is ideal for small-particle Reynolds numbers when fluid particles behave similar to solid particles and for flow around a single sphere. Therefore, this drag model is suitable as the particles of salbutamol sulfate can be idealized as spheres with a constant diameter.⁽¹⁶⁾

The deposition was determined through custom FORTRAN and MATLAB code. The FORTRAN code was used to extract the final position of each of the 10,000 particles. These positions were exported to MATLAB and analyzed using a script that determined if the final position of the particles intersected with the geometry of the spacer or exited the domain.

Lagrangian particle tracking

ANSYS CFX has the functionality to perform Lagrangian particle tracking, ideal for particles with small diameters in multiphase flow.⁽¹⁷⁾ The three-dimensional Lagrangian equation states that

$$\frac{du_{p,i}}{dt} = \frac{(u_{f,i} - u_{p,i})}{\tau_p} - g_i \left(1 - \frac{\rho_f}{\rho_p}\right) \quad (4)$$

where $u_{p,i}$ is the particle velocity components (m/s), $u_{f,i}$ is the instantaneous fluid flow components at the particle location (m/s), and g_i is the gravitational components (m/s²).

The relaxation time of the particle can be expressed as follows:

$$\tau_p = \frac{\rho_p d_p^2}{18\mu\alpha} \quad (5)$$

where

$$\alpha = 1 + 0.15Re_p^{0.687} \quad (6)$$

Re_p is the particle Reynolds number.

When RANS equations are used, each particle has an instantaneous velocity divided into two components, mean and fluctuating:

$$u_{f,i} = \bar{u}_{f,i} + u'_{f,i} \quad (7)$$

Mean flow tracking

Mean flow tracking conducts simulations without modeling, which allows for the fluctuating component ($u'_{f,i}$) of the instantaneous fluid velocity to be considered zero. The implementation of mean flow tracking assumes deposition to only occur due to the average flow.

Turbulent tracking

Turbulent tracking, also known as the random walk model, considers both the mean and fluctuating components of the instantaneous velocity. The inclusion of the fluctuating component results in particle dispersion in turbulent flow since particles can follow independent tracks at each injection point.

To model this turbulent particle dispersion, each particle is assumed to interact with eddies as it travels throughout the domain. Each eddy has a characteristic length, lifetime, and velocity. When a particle interacts with an eddy, the fluctuating component of the instantaneous fluid velocity is assumed to be equal to the fluctuating velocity of the eddy. This causes the fluctuating velocity ($u'_{f,i}$) to dominate. A particle ends its interaction with an eddy if the lifetime of the eddy is exceeded or the particle travels the eddy length. At this point, the particle is assumed to enter another new eddy.

To implement turbulent tracking, an eddy viscosity ratio must be first selected. This eddy viscosity ratio can be defined as follows:

$$\frac{\mu_t}{\mu} \quad (8)$$

where μ_t is the turbulent viscosity and μ is the molecular dynamic viscosity.

This ratio determines how strong the influence of turbulent viscosity is compared to dynamic viscosity. For simulations involving turbulent tracking, this ratio was set to the default value of 5.

Results and Discussion

Experimental results

Experiments were conducted to assess the regional deposition of salbutamol sulfate in the Volumatic and OptiChamber spacers. Figure 10 shows the regional deposition of salbutamol sulfate in the spacers at inspiratory flow rates of 30, 45, and 60 L/min.

For higher flow rates, the Volumatic and OptiChamber spacers allowed a slightly greater amount of medication to reach the patient. The amount of medication reaching the patient is indicated by the decrease in deposition in the spacer and increase in deposition in the filter for higher flow rates. Figure 10 shows a greater amount of deposition in the lower half of both spacers for all flow rates. This

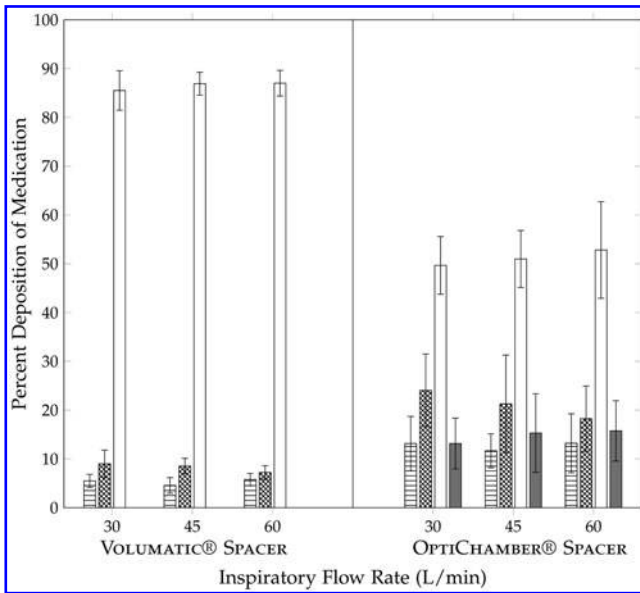


FIG. 10. Experimental results of the percent deposition of medication in the upper and lower regions of the Volumatic and OptiChamber spacers. ■ Upper half of spacer; ▨ lower half of spacer; □ filter; ■ valve and mouthpiece.

nonsymmetrical deposition was expected due to the downward spray angle deflection from the pMDI itself as reported by Crosland et al.⁽⁴⁾

For higher flow rates, a greater amount of deposition was also found to occur at the distal half of the spacers as shown in Figure 11. It should be noted that the distal half of the OptiChamber spacer included deposition in the valve and mouthpiece of the spacer. For the OptiChamber, this result suggested that more medication is likely to impinge in the valve portion of the spacer at higher flow rates before reaching the patient, significantly reducing the amount of

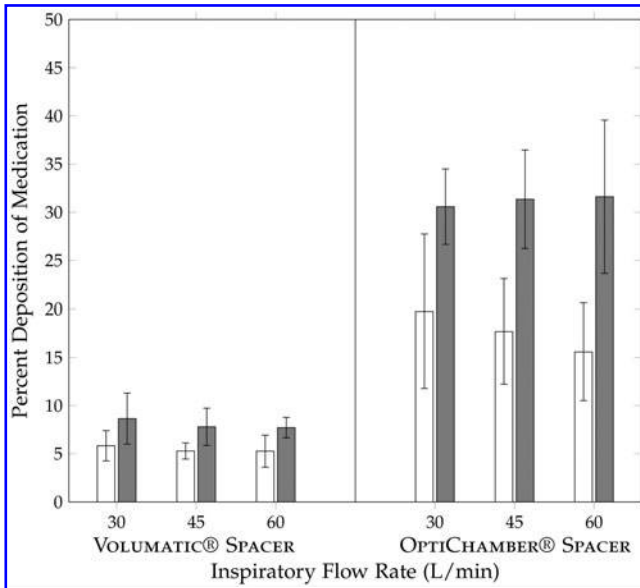


FIG. 11. Experimental results of the percent deposition of medication in the proximal and distal regions of the Volumatic and OptiChamber spacers. □ Near half of spacer; ■ distal half of spacer.

medication delivered. These deposition patterns were also demonstrated by the Volumatic spacer, however, the amount of distal deposition was not so extreme. It is conjectured that more medication would reach a patient using the Volumatic spacer due to the absence of a valve.

For both spacers, it is apparent that the amount of distal deposition increased with an increasing flow rate, but the amount of medication reaching the patient seemed to remain relatively constant. Since these trends show more distal deposition with a greater flow rate, it is possible that a greater flow rate (i.e., larger and deeper breaths by the patient) will not allow for more delivered medication but cause deposition in the distal region of the spacer as opposed to the proximal region. Since the amount of deposited medication was essentially shifted from the proximal to distal half of the spacer due to the higher flow rate, this could provide an explanation as to why the amount of delivered medication remained consistent despite variations in the flow rate.

Correlated *t*-test

Due to the large amount of variance in the experimental results for assessing distal and proximal deposition, a correlated *t*-test was conducted to ensure the reported results were statistically different for both the OptiChamber and Volumatic spacers.

The null hypothesis for the first *t*-test in this analysis was that the mean difference between distal and proximal deposition for each trial is zero. A *t* value was calculated using the following equation:

$$t = \frac{M - \mu}{S_M} \quad (9)$$

where *M* is the sample mean, μ is assumed 0, and s_M is the standard error of the mean.

Similarly, a second *t*-test was conducted to ensure that the differences between the lower and upper deposition were statistically different. The null hypothesis for this second *t*-test in this analysis was that the mean difference between lower and upper deposition for each trial is zero.

Tables 1 and 2 list the *t* values and corresponding two-tailed probability values (found using appropriate *z*-tables) for each flow rate and spacer.

Using an alpha of 0.05, indicating a 95% confidence interval, each computed mean are significantly different from 0. Therefore, the lower deposition found from this experimental analysis can be said to be statistically higher than the upper deposition. In addition, the distal deposition can be said to be statistically higher than the near deposition.

Numerical results

For the numerical analysis, transient simulations were conducted to study the behavior of salbutamol sulfate in the Volumatic and OptiChamber spacers. Simulations incorporating the downward spray angle developed over the actuation of the pMDI were carried out at 30, 45, and 60 L/min. Using URANS and particle tracking, it was possible to find where particles deposited within the spacer.

Figure 12 displays the spray angle over 100 milliseconds for a steady inhalation flow rate of 60 L/min. This figure shows how the spray velocity along the center of the spacer reduces considerably throughout the actuation of the puffer.

TABLE 1. CALCULATED t VALUES AND TWO-TAILED PROBABILITY TO PROVE STATISTICAL DIFFERENCE BETWEEN THE EXPERIMENTAL DEPOSITION FOUND ON THE LOWER VERSUS UPPER REGIONS AND DISTAL VERSUS NEAR REGIONS OF THE OPTICHAMBER SPACER FOR EACH CORRESPONDING FLOW RATE

Flow rate (L/min)	OptiChamber [®] spacer					
	Standard error of mean (s_M)		t Value		Two-tailed probability (p)	
	Lower–upper difference	Distal–near difference	Lower–upper difference	Distal–near difference	Lower–upper difference	Distal–near difference
30	2.39	2.87	4.57	3.77	0.00044	0.0021
45	2.09	2.35	4.23	5.81	0.00085	0.000045
60	2.16	3.98	2.33	4.03	0.035	0.0012

With an increased distance from the actuator nozzle, the velocity experiences a significant reduction. Therefore, the use of a spacer would minimize oral and oropharyngeal deposition (from inertial deposition) due to the lower velocity of the spray plume, providing slower moving particles that are easier to inhale.

The 10,000 particles released into the domain were tracked over the duration of the simulation. Their paths were tracked to locate the point at which the medication would deposit. A sample of the mean flow particle tracks for an inhalation flow rate of 30 L/min in the Volumatic spacer is displayed in Figure 13.

Turbulent tracking was also performed to find the most suitable tracking option. For the Volumatic spacer, the deposition results of turbulent tracking showed deposition mainly in the spacer with only a fraction of the medication (50%–60%) leaving the spacer. This result suggested that a significant amount of the medication does not reach the patient if the particles in the Volumatic spacer are assumed to interact with eddies as they travel through the domain. Furthermore, when compared to the experimental data, mean flow tracking better reflected experimental results of the Volumatic spacer.

On the contrary, when considering the OptiChamber, experimental data were better reflected through turbulent tracking. Mean flow tracking for the OptiChamber displayed an excessive amount of inhaled medication (upward of 70%) and a severe underprediction of the amount of medication depositing inside the spacer itself. Turbulent tracking better reflected the experimental deposition results, displaying that around 55% of the medication will be inhaled by the patient. The numerical results for the OptiChamber showed an in-

crease in deposition on the valve portion of the OptiChamber with higher flow rates, suggesting that more deposition will be expected in the distal portion of the spacer if a higher inhalation flow rate is used.

Figure 14 displays the mean flow tracking results for both the Volumatic and OptiChamber spacers. As displayed, implementing mean flow tracking for the OptiChamber resulted in little to no deposition on the upper and lower portions of the spacer. In addition, Figure 15 displays the turbulent tracking results for both spacers. For the Volumatic spacer, the turbulent tracking results led to a substantial underprediction of the amount of medication reaching the patient while displaying an overprediction of the deposition of medication inside the spacer. It should be noted that turbulent tracking results for the OptiChamber at an inhalation flow rate of 45 L/min displayed a slightly lower amount of medication delivered to the patient and an increase in deposition inside the spacer itself when compared to the other flow rates. Figure 16 displays the amount of medication deposited in the proximal and distal regions of the OptiChamber. As expected, Figure 16 displays a shift of the medication into the distal region with higher flow rates. However, it appears that at 45 L/min, there is more medication depositing in the upper distal region of the spacer. It is conjectured that at 45 L/min, the medication does not have enough velocity to travel the length of the spacer and, as such, will deposit and settle just before the valve (i.e., in the distal region). At 60 L/min, this medication is traveling at a high enough velocity to travel the length of the spacer but will impinge on the valve resulting in an increased deposition in the valve itself and a lower amount of medication reaching the outlet of the spacer.

TABLE 2. CALCULATED t VALUES AND TWO-TAILED PROBABILITY TO PROVE STATISTICAL DIFFERENCE BETWEEN THE EXPERIMENTAL DEPOSITION FOUND ON THE LOWER VERSUS UPPER REGIONS AND DISTAL VERSUS NEAR REGIONS OF THE VOLUMATIC SPACER FOR EACH CORRESPONDING FLOW RATE

Flow rate (L/min)	Volumatic [®] spacer					
	Standard error of mean (s_M)		t Value		Two-tailed probability (p)	
	Lower–upper difference	Distal–near difference	Lower–upper difference	Distal–near difference	Lower–upper difference	Distal–near difference
30	0.57	0.53	6.08	5.32	0.00030	0.00071
45	0.72	0.61	5.52	4.13	0.00056	0.0033
60	0.12	0.31	12.18	7.89	<0.000010	0.000048

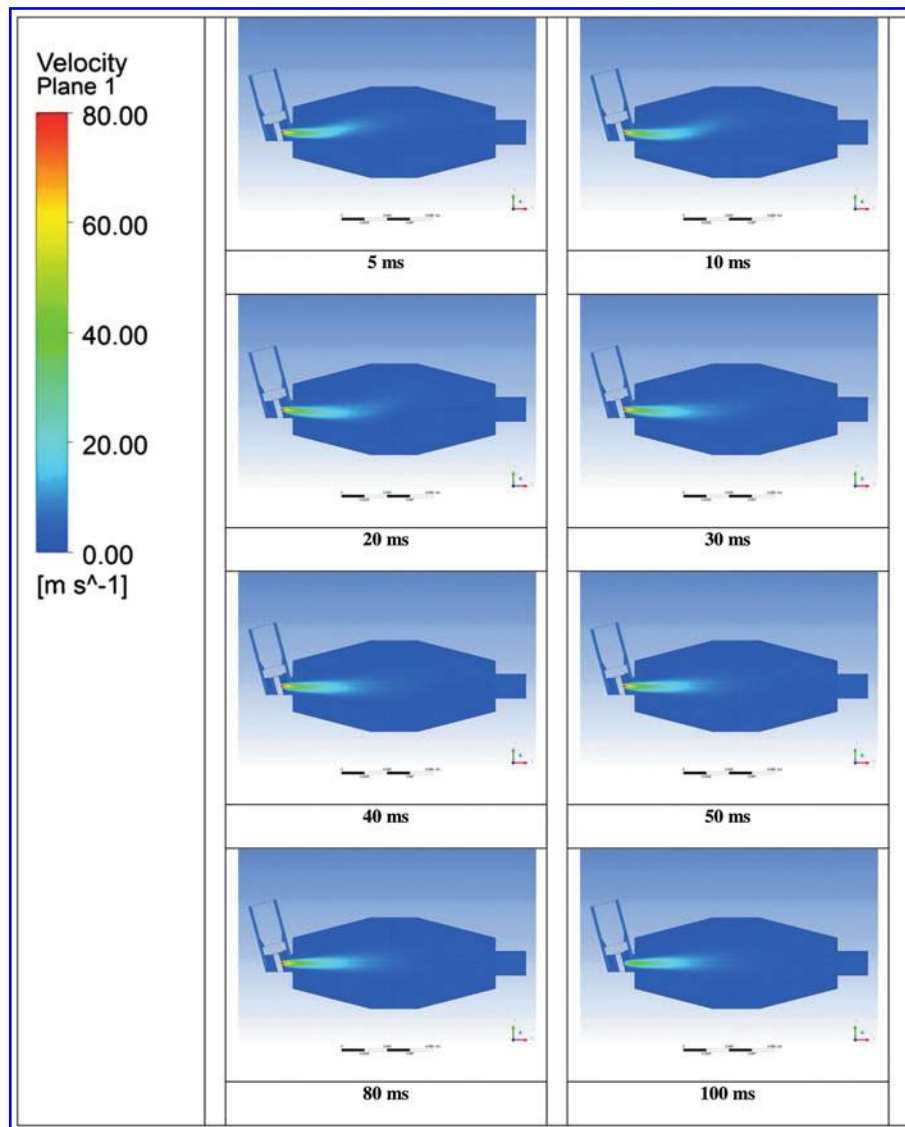


FIG. 12. Visualization of the fluctuation spray angle from the pMDI over 100 milliseconds for an inhalation rate of 60 L/min.

From Figures 14 and 15, it is evident that the mean flow and turbulent tracking results for the Volumatic and OptiChamber spacers, respectively, show generally good agreement against the experimental data for all inhalation rates.

Therefore, based on experimental results, deposition in the Volumatic spacer is more likely due to the inertial impaction from the downward spray angle of the actuator (as seen in mean flow tracking) and not due to the turbulence from the flow. Consequently, deposition in the OptiChamber spacer is more likely due to the turbulence from the flow.

Conclusions

Measurements of the deposition of a pMDI aerosol spray, salbutamol sulfate, in the Volumatic and OptiChamber spacers indicated that an increase in inhalation flow rate (30–60 L/min) will only result in a slight increase in the amount of medication provided to a patient as studied in this research. Experimental results demonstrated that more deposition is expected in the distal portion of the spacers with an increase in

the inhalation flow rate. As such, it seems that a variation of flow rate will not affect the amount of medication delivered to a patient but rather it will alter the location and amount of deposition in the spacer. Simulations of both the Volumatic and OptiChamber also showed similar results. For both spacers, the deposition of pMDI aerosol spray was found to be higher in the lower half of the spacer when compared to the upper half for all inhalation rates studied.

This was expected due to the variation of the pMDI spray angle deflecting downward (from 0° to -6° of the spray axis) and upward, realigning with the spray axis as studied by Alhegagi and Matida,⁽⁹⁾ Alhegagi,⁽¹⁰⁾ Matida and Alhegagi,⁽¹⁴⁾ and Crosland et al.⁽⁴⁾

Numerical analysis of the Volumatic spacer, performed to simulate the experiments, showed relatively good agreement with the experimental findings when using mean flow tracking. This suggests that inertial impaction is likely to be the dominant method of deposition. Conversely, numerical analysis of the OptiChamber spacer showed better agreement with experimental findings when using turbulent

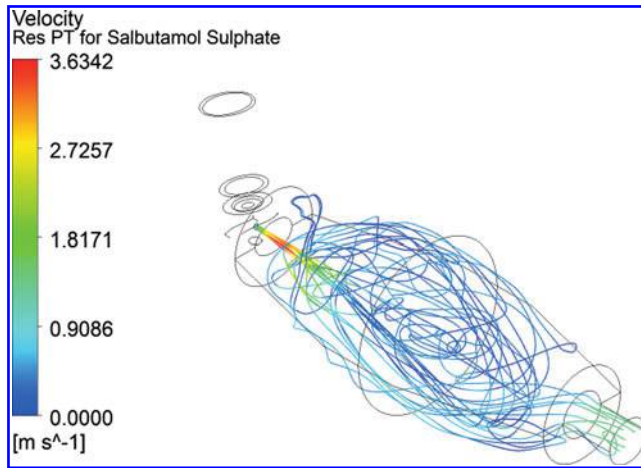


FIG. 13. Visualization of the salbutamol sulfate particle tracks in the Volumatic spacer at an inhalation rate of 30 L/min.

tracking. This suggests that turbulence is likely to be the dominant method of deposition in the OptiChamber.

Based on the experimental and numerical analysis conducted, it would be beneficial for a spacer to not have a valve or filter on its distal end but rather, an opening with a large enough diameter to allow the medication to exit with spacer with minimal disturbance (i.e., reduce the sharpness in the degree of convergence to a nozzle). At higher flow rates, a valve or filter would only act to impinge medication and reduce the amount delivered. Also, due to the downward spray angle, a spacer that considered the -6° deflection in its design would result in less deposition in the lower portion of the spacer. This could be achieved by implementing a nonsymmetrical design of the spacer itself, curving the bottom portion to provide an increased distance between the nozzle of the pMDI and the bottom surface of the spacer.

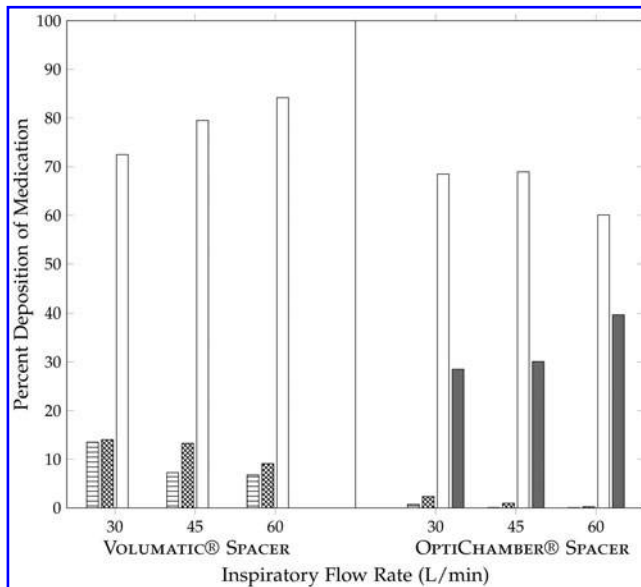


FIG. 14. Numerical results of the deposition of salbutamol sulfate in the regions of the Volumatic and OptiChamber found through mean flow tracking. ■ Upper half of spacer; ▨ lower half of spacer; □ filter; ■ valve.

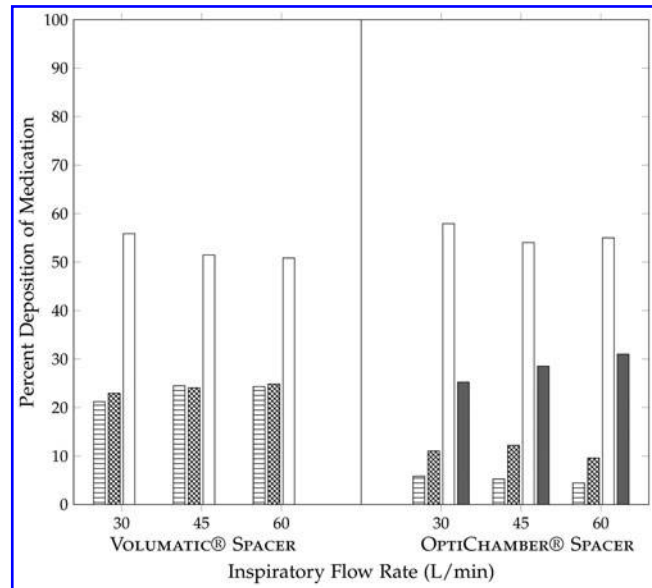


FIG. 15. Numerical results of the deposition of salbutamol sulfate in the regions of the Volumatic and OptiChamber found through turbulent tracking. ■ Upper half of spacer; ▨ lower half of spacer; □ filter; ■ valve.

From these results, it also seems as if the flow rate will have a minimal effect on the amount of medication delivered to a patient. However, the flow rate will affect the location of deposition of medication inside the spacer itself. Therefore, to deliver more medication to a patient, it is important to consider a recommended flow rate at which the spacer should be used. A bulbous spacer, which does not interrupt the streamlines of the medication, would be more beneficial than one with sharp edges.

To develop this research further, numerically, a large eddy simulation (LES) could be used to further capture the

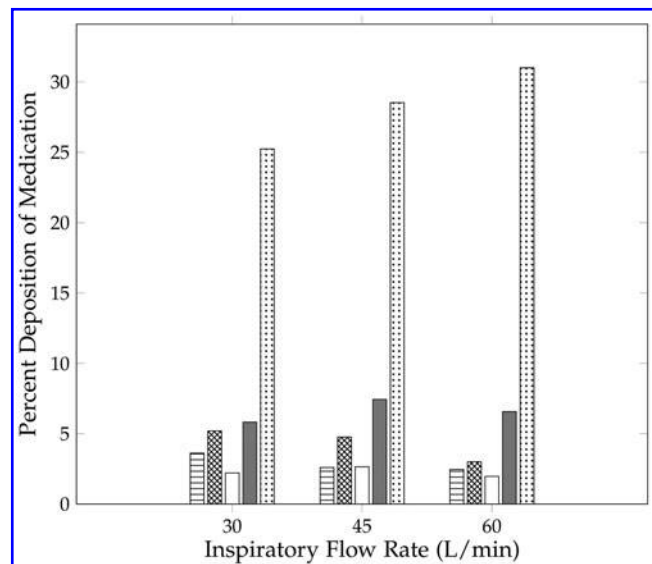


FIG. 16. Numerical results of the deposition of salbutamol sulfate in the proximal and distal regions of the OptiChamber found through turbulent tracking. ■ Proximal upper; ▨ proximal lower; □ distal upper; ■ distal lower; ▩ valve.

behavior of the flow and improve the accuracy of the simulation of eddies as in Matida et al.^(18,19)

Acknowledgments

The authors thank NSERC for providing support throughout this research and Steve Truttman for providing the equipment.

Author Disclosure Statement

No competing financial interests exist.

References

1. Dodge RR, and Burrows B: The prevalence and incidence of asthma and asthma-like symptoms in a general population sample. *Am Rev Respir Dis.* 1980;122:567–575.
2. Boulet L, Becker A, Bérubé D, Beveridge R, and Ernst P: Canadian asthma consensus report, 1999. *Can Med Assoc J.* 1999;161:4.
3. Newman S: Principles of metered-dose inhaler design. *Respir Care.* 2005;50:1177–1190.
4. Crosland B, Johnson M, and Matida E: Characterization of the spray velocities from a pressurized metered-dose inhaler. *J Aerosol Med Pulm Drug Deliv.* 2009;22:85–97.
5. Pauwels R, Newman S, and Borgstrom L: Airway deposition and airway effects of antiasthma drugs delivered from metered-dose inhalers. *Eur Respir J.* 1997;10:2127–2138.
6. Thorsson L, Edsbacker S, and Conradson T: Lung deposition of budesonide from turbuhaler is twice that from a pressurized metered-dose inhaler p-mdi. *Eur Respir J.* 1994;7:1839–1844.
7. Broeders M, Sanchis J, Levy M, Crompton G, and De-khuijzen P: The admit series-issues in inhalation therapy. 2. Improving technique and clinical effectiveness. *Prim Care Respir J.* 2009;18:76–82.
8. Barry P, and O'Callaghan C: The optimum size and shape of spacer devices for inhalational therapy. *J Aerosol Med.* 1995;8:303–305.
9. Alhegagi G, and Matida E: Non-symmetrical pMDI deposition measurement in add-on spacers. [Abstract]. Presented at the American Association for Aerosol Research 29th Annual Conference, Portland, Oregon, October, 2010.
10. Alhegagi G: Pressurized metered-dose inhaler (pMDI) aerosol deposition measurements in add-on spacers. Diss. Carleton University, Ottawa, 2009.
11. Newman S: Spacer devices for metered dose inhalers. *Clin Pharmacokinet.* 2004;43:349–360.
12. Menter F: Two-equation eddy-viscosity turbulence models for engineering applications. *AIAA J.* 1994;32:1598–1605.
13. Anderson J: *Computational Fluid Dynamics.* Springer, New York, p. 101, 1995.
14. Matida E, and Alhegagi G: Numerical simulation of pMDI aerosol deposition in add-on spacers. [Abstract]. Presented at the American Association for Aerosol Research 29th Annual Conference, Portland, Oregon, 2010. McGraw Hill, Inc.
15. Sprigge E: Non uniform deposition of pMDI aerosol in a large volume spacer. Diss. Carleton University, Ottawa, 2014.
16. Gryczka O, Heinrich S, Deen N, Van Sint Annaland M, Kuipers J, Jacob M, and Mörl L: Characterization and cfd-modeling of the hydrodynamics of a prismatic spouted bed apparatus. *Chem Eng Sci.* 2009;64:3352–3375.
17. Guo B, Fletcher D, and Langrish T: Simulation of the agglomeration in a spray using lagrangian particle tracking. *Appl Math Model.* 2004;28:273–290.
18. Matida E, Finlay W, Breuer M, and Lange C: Improving prediction of aerosol deposition in an idealized mouth using large-eddy simulation. *J Aerosol Med.* 2006;19: 290–300.
19. Matida E, Finlay W, Lange C, and Grgic B: Improved numerical simulation of aerosol deposition in an idealized mouth-throat. *J Aerosol Sci.* 2004;35:1–19.

Received on August 10, 2015
in final form, March 30, 2016

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